

Colon and Anorectal Cancer After Pelvic Irradiation

SHU-WEN JAO, M.D., ROBERT W. BEART, JR., M.D., HERBERT M. REIMAN, M.D.,
LEONARD L. GUNDERSON, M.D., DUANE M. ILSTRUP, M.S.

Jao S-W, Beart RW Jr, Reiman HM, Gunderson LL, Ilstrup DM. Colon and anorectal cancer after pelvic irradiation. *Dis Colon Rectum* 1987;30:953-958.

Seventy-six cases of colon or anorectal cancer after pelvic irradiation for other malignant or benign lesions were reviewed. The patients were 13 men and 63 women with a mean age of 65 years; 67 percent had received irradiation for gynecologic malignancy. The cancer developed at a mean of 15.2 years after irradiation (peak frequency between five and ten years); 85 percent of the patients had a mild to prominent radiation reaction around the cancer. Of the 72 adenocarcinomas, 26 percent were mucinous. Only 17 percent of patients presented with symptoms of radiation proctitis, and the mean radiation dosages were not high. High radiation dosage and severe radiation damage may not be essential for radiation-associated colorectal cancer. The overall five-year survival rate was 48 percent. Close surveillance of the colon and anorectal regions of these high-risk patients at five years after irradiation is indicated. [Key words: Low-dose pelvic irradiation; Radiation proctitis; Postirradiation carcinoma; Colon carcinoma]

RADIATION HAS BEEN identified as a possible carcinogen in skin, thyroid, bone marrow, breast, lung, salivary gland, and bladder. The occurrence of colon or anorectal cancer after pelvic irradiation also has been reported, but the series have been small. Most cases reported were in women who had had previous irradiation for gynecologic cancer.

The authors have reviewed their experience with

*From the Section of Colon and Rectal Surgery,
the Section of Surgical Pathology,
the Division of Therapeutic Radiology, and the
Department of Medical Statistics and Epidemiology,
Mayo Clinic and Mayo Foundation,
Rochester, Minnesota*

cancer superimposed upon an irradiated colon and anorectum in an effort to identify the characteristics and natural history of this lesion.

Materials and Methods

The authors reviewed the records of patients with colon or anorectal cancer who had surgical treatment at the Mayo Clinic and a history of prior pelvic or abdominal irradiation for other malignant or benign lesions. Patients whose colon or anorectal cancer developed within two years after irradiation were excluded from this series. The radiation method, dosage, and interval between irradiation and subsequent appearance of the cancer development were recorded. The tissue slides were reviewed; the tumor site, cell type, staging, and radiation effects on normal tissue were recorded. Radiation effects in the bowel wall included submucosal fibrosis, telangiectasia, endothelial proliferation, and hyalinization of blood vessels and were quantitated as none, mild, or prominent. Follow-up information was obtained from each patient by personal interview or letter. Patient survival was estimated using the nonparametric method of Kaplan and Meier.¹

Received for publication May 11, 1987.

Address reprint requests to Dr. Beart: Section of Colon and Rectal Surgery, Mayo Clinic, Scottsdale, 13400 East Shea Boulevard, Scottsdale, Arizona 85288.

Dr. Jao is a visiting clinician from the Section of Colon and Rectal Surgery, Department of Surgery, National Defense Medical Center and Tri-Service General Hospital, Taipei, Taiwan, R.O.C.

TABLE 1. Location of Colon or Anorectal Cancer, by Reason for Previous Irradiation

| Reason for Irradiation | Location of Subsequent Cancer | | | | | | | Total Patients |
|------------------------|-------------------------------|-----------|------------|------------|---------|--------|------|----------------|
| | Cecum | Ascending | Transverse | Descending | Sigmoid | Rectum | Anus | |
| Carcinoma of | | | | | | | | |
| Cervix | 3 | 2 | 1 | | 11 | 9 | 4 | 30 |
| Uterus | 6 | 2 | 2 | | 2 | 4 | | 16 |
| Ovary | 3 | | | | 2 | | | 5 |
| Bladder | | | | | 2 | 2 | | 4 |
| Prostate | 1 | | | | 2 | 1 | | 4 |
| Lymphoma | 2 | 1 | 1 | | 1 | 2 | | 7 |
| Menorrhagia | | | | | 2 | 2 | | 4 |
| Endometriosis | | | | | 2 | | | 2 |
| Low back pain | | | | | 1 | | | 1 |
| Skin itching | | | | | 1 | | | 1 |
| Sarcoma | | | | | 1 | | | 1 |
| TOTAL | 15 | 5 | 4 | - | 27 | 20 | 4 | 75 |

Results

Seventy-six cases were identified. The patients were 13 men and 63 women, with a mean age of 65 years (range, 39 to 88 years). The chief reasons for previous pelvic irradiation (Table 1) were cervical (39 percent) and uterine (21 percent) carcinoma. Eight patients had received radiotherapy for benign lesions. The cancer developed at a mean of 15.2 years (range, two to 41 years) after irradiation (Fig. 1). Forty-six patients (61 percent) had had their

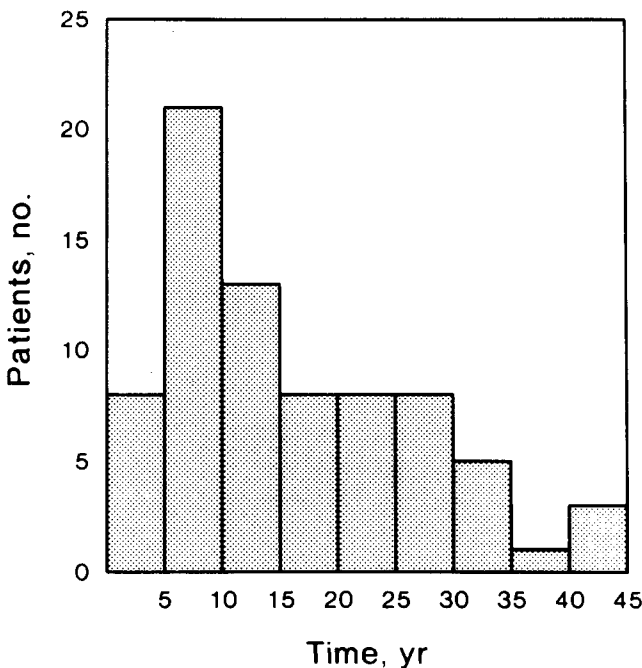


FIG. 1. Interval between irradiation and development of colon or anorectal cancer. No data available for one patient.

radiation exposure more than ten years before the cancer was detected. Fifty-three patients (70 percent) had had radiotherapy at the authors' clinic; radiation information was available for 67 patients (88 percent) (Table 2).

Only 13 patients (17 percent) had clinical manifestations of radiation proctitis. There were 72 adenocarcinomas (26 percent mucinous), two basaloid carcinomas, and two squamous cell carcinomas of the anus. Sixty-eight (89 percent) patients underwent a major operation for resection of tumor. Three patients underwent colostomy only because their disease was advanced. Three patients had local resection for a small anorectal cancer. Two patients had polypectomy for focal cancer. Seventeen patients (22 percent) had postoperative complications, including operative death in four (5 percent).

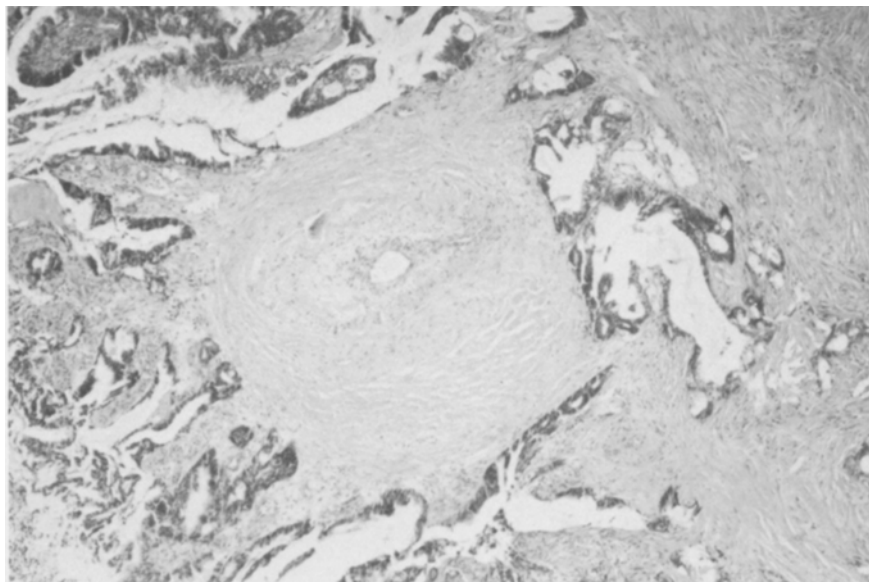
Upon reviewing the tissue slides, 52 cases (68 percent) with a prominent radiation reaction around the cancers were found (Figs. 2-5); 13 cases (17 percent) had only mild radiation reaction, six cases (8 percent) had no significant radiation reaction, and in five cases (7 percent) not enough tissue was available for diagnosis of the radiation effects. The primary tumor sites in the 11 cases with no significant reaction or lack of tissue were the rectum in nine, the sigmoid in one, and the cecum in one.

All patients were followed postoperatively for four

TABLE 2. Methods and Dosages of Radiotherapy in 67 Patients With Available Data

| Method | Number of Patients | Dose (Range) |
|---------------------------|--------------------|----------------------------------|
| External x-ray | 29 | 120-6,000 rad |
| Radium | 11 | 900-9,125 mg hr |
| Cesium | 4 | 1,056-2,127 mg hr |
| Radium and external x-ray | 23 | 834-8,700 mg hr 555-4,500 rad |

FIG. 2. Hyalinized vessel with marked endothelial proliferation surrounded by dense fibrosis and mucinous adenocarcinoma (hematoxylin and eosin; $\times 120$).



months to 29 years (mean, 6.3 years; median 3.1, years). The five-year survival rates are shown in Table 3. The overall five-year survival rate was 48 percent (Fig. 6). Nineteen tumors (26 percent) of the 72 adenocarcinomas were the mucinous type. There was no evidence of increased radiation doses or proctitis in this group. Sixty-nine percent of the tumors were favorably staged (Astler-Coller A, B₁, or B₂). The 30-day operative mortality was 6 percent and the morbidity 24 percent.

Discussion

Slaughter and Southwick² first reported two colon cancers and one anal cancer that developed in the pres-

ence of radiation injury. Smith³ reported three additional cases in 1962. Since that time, there have been reports of similar findings,⁴⁻¹⁹ but most of them were case reports. Until now, only 52 cases have been reported in the English literature (Table 4). The largest series was reported by Castro *et al.*¹¹ in 1973, with a total of 26 patients. They found that 58 percent of the patients had symptomatic, histologic, and clinically documented chronic radiation proctocolitis at the site of subsequent tumor; 69 percent of the patients had a postirradiation interval of more than ten years; a high percentage (58 percent) of mucinous adenocarcinoma was found; overall and determinate five-year survivals were poor, 20 percent and 22 percent,

FIG. 3. Prominent medial elastosis with endothelial proliferation and narrowing of the lumen (same vessel as in Fig. 2) (elastic-van Gieson stain; $\times 300$).

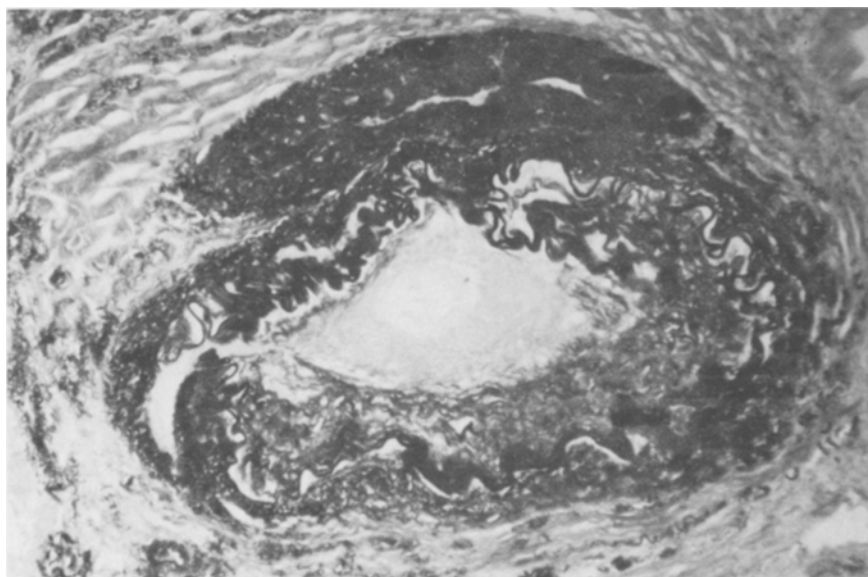
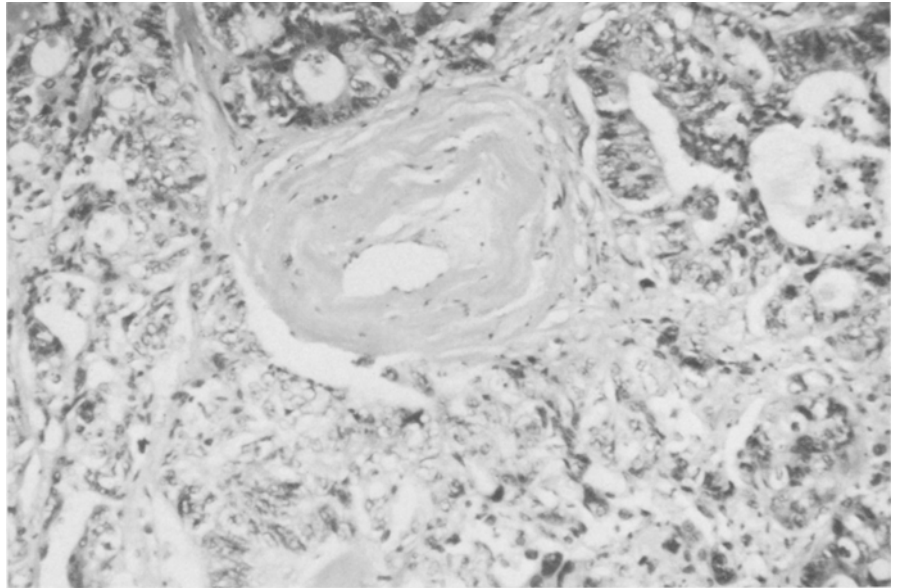


FIG. 4. Hyalinized vessel in previous radiation field surrounded by adenocarcinoma (hematoxylin and eosin; $\times 300$).



respectively. Most reports demonstrated a close relationship between radiation effects and colorectal cancer but lacked strong evidence that the cancer was induced by the irradiation.

Other series with a long-term follow-up demonstrated an increased incidence of colon or rectal cancer after pelvic irradiation.²⁰⁻²⁶ Although a patient who has had one malignancy may be at increased risk to develop a second malignancy, a controlled study by Reimer *et al.*²² found that ovarian cancer patients who had radiotherapy had an increased risk of colon cancer compared to those ovarian cancer patients who did not have radiotherapy, and the risk became more evident in patients followed for

more than five years. In addition, patients who had had radiotherapy for benign conditions still had a significantly increased risk of colorectal cancer when compared with the normal population.^{21, 23-25} The early mortality studies of atomic bomb survivors in Japan showed little to suggest a relationship between irradiation and colon cancer,²⁷ but long-term follow-up has demonstrated significantly increased mortality from colon cancer.²⁸ Radiation also has been shown to induce colon cancer in animal studies.^{29, 30}

Black and Ackerman⁴ concluded that radiation-induced carcinomas of rectosigmoid show: 1) an interval of more than ten years between radiotherapy and the diagnosis of

FIG. 5. Anal basaloid carcinoma adjacent to telangiectatic vessel within dense fibrosis (hematoxylin and eosin; $\times 750$).

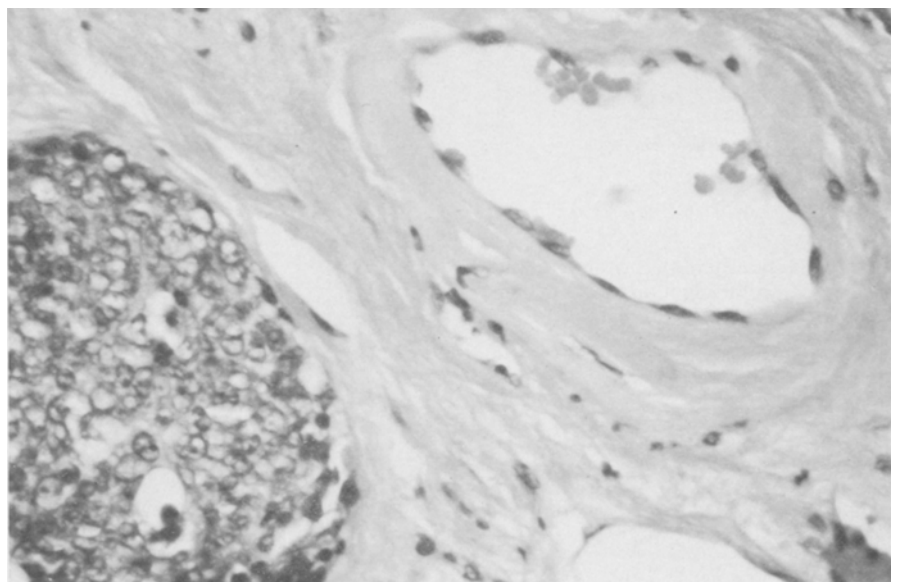


TABLE 3. Five-Year Survival Rates, by Stage (Astler-Coller)

| Stage | Patients | | Overall 5-year Survival Rate, Percent |
|----------------|----------|---------|--|
| | No. | Percent | |
| A | 10 | 13 | 90 |
| B ₁ | 11 | 15 | 91 |
| B ₂ | 32 | 42 | 45 |
| C ₁ | 1 | 1 | - |
| C ₂ | 9 | 12 | 17 |
| D | 13 | 17 | 8 |
| TOTAL | 76 | 100 | 48 |

carcinoma; 2) relatively large radiation exposure to large bowel; and 3) severe radiation damage around the cancer. MacMahon and Rowe⁹ also listed three high-risk factors for irradiation-associated colon cancer: 1) proctitis early after irradiation; 2) subsequent secondary proctitis; and 3) stenosis or induration of the rectovaginal septum. These three factors all relate to high-dose irradiation.

In the present series, the mean interval from radiation to diagnosis of carcinoma was 15.2 years, and 61 percent of the patients had an interval of more than ten years. The peak frequency was between five and ten years. Previous reports²⁻²⁰ also show a higher proportion of patients developing cancer between five and ten years after irradiation. Most of the present patients had radiation reactions around the cancer. These reactions may be present for a long period. Three patients had their irradiation 41 years before diagnosis of the new malignancy: two still had prominent radiation reaction and one had a mild radiation reaction. Apparently, the increased risk of development of colon or anorectal cancer may start at five years and persist to more than 40 years after irradiation.

Although Black and Ackerman⁴ and MacMahon and Rowe⁹ suggested that high-dose radiation or severe radiation damage is essential for the induction of colorectal cancer, Palmer and Spratt²⁵ found that patients who had received low irradiation dosage for benign gynecologic conditions had a greater chance (3.32 percent) of developing rectal cancer than those who had received high-dose irradiation (1.4 percent) to treat cancer of the cervix. They concluded that the relatively low irradiation dosage caused some growth-stimulating influence that the high dosage did not cause. Rubin *et al.*²⁴ also mentioned:

The finding that the development of cancer was greater in the low dose irradiation group has suggested... that reaction to radiation injury leads to hyperplasia and then to neoplasia which may not occur after high doses; *i.e.*, a large dose of radiation may eliminate the regenerative capacity of tissues completely.

Denman *et al.*²⁹ found that doses of 4500 rad caused the highest incidence of colon cancer in rats, compared with doses of 2500, 3500, 5500, and 6500 rad. In the present series, only 17 percent of patients had clinical symptoms of radiation proctitis. This observation suggests that the large bowel was exposed to relatively low doses of irradiation.

TABLE 4. The 52 Cases Reported by 18 Authors

| Author | Year | Cases | Reference |
|-------------------------|------|-------|-----------|
| Slaughter and Southwick | 1957 | 3 | 2 |
| Smith | 1962 | 3 | 3 |
| Black and Ackerman | 1965 | 1 | 4 |
| Quan | 1968 | 2 | 5 |
| Pemberton and Lendrum | 1968 | 1 | 6 |
| Localio <i>et al.</i> | 1969 | 1 | 7 |
| DeCose <i>et al.</i> | 1969 | 1 | 8 |
| MacMahon and Rowe | 1971 | 6 | 9 |
| Bhagabati and Zaman | 1973 | 1 | 10 |
| Castro <i>et al.</i> * | 1973 | 26 | 11 |
| Cunningham and Wilhoite | 1973 | 1 | 12 |
| Qizilbash | 1974 | 1 | 13 |
| Greenwald <i>et al.</i> | 1978 | 1 | 14 |
| O'Connor <i>et al.</i> | 1979 | 2 | 15 |
| Sabio <i>et al.</i> | 1979 | 1 | 16 |
| Martins <i>et al.</i> | 1980 | 1 | 17 |
| Shamsuddin and Elias | 1981 | 1 | 18 |
| Echave <i>et al.</i> | 1982 | 1 | 19 |

*Includes two cases reported by Quan (1968).⁵

Castro *et al.*¹¹ reported an incidence of mucinous adenocarcinoma of 58 percent in their series, which is higher than the usual distribution (10 percent); 92 percent of these patients had clinical or histologic evidence of radiation proctitis. In the authors' series, 19 (26 percent) mucinous adenocarcinomas were found in 72 patients with adenocarcinoma. There was no evidence of an increased incidence of radiation proctitis in this group. This percentage is lower than that in Castro's report but is still much higher than the normal distribution. Denman *et al.*²⁹ found that all the colon cancers induced by radiation in rats were mucinous adenocarcinoma. These findings suggest that the abnormally high proportion of mucinous adenocarcinoma found in the authors' and Castro's patients may relate to a radiation-induced origin.

In the previous reports, most of the cases were limited

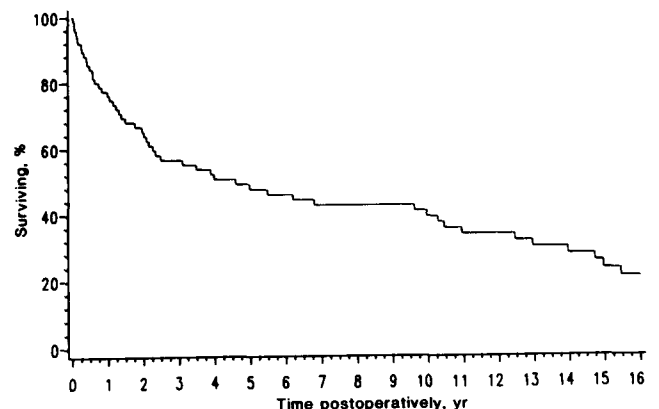


FIG. 6. Postoperative survival for colon or anorectal cancer after pelvic irradiation.

to women with a history of gynecologic cancer, and most of the large bowel cancers were located in the sigmoid colon or rectum. In the present series, only 67 percent of patients had a history of gynecologic cancer, and there were 13 male patients. Most of the male patients had received previous irradiation for cancer of the bladder or prostate or for lymphoma. Only two male patients with radiation-associated colon cancer have been reported previously.^{2,6} There have been no previous reports of colorectal cancer after irradiation for cancer of the bladder or prostate or for lymphoma.

There have been five right-side colon cancers in previous reports, and all were cecal cancers. Four of these patients had had irradiation for carcinoma of an ovary or the uterus; only one had carcinoma of the cervix. The present series included 20 right-side colon cancers (15 of the cecum and five of the ascending colon), and 11 of these patients had had irradiation for carcinoma of the ovary or uterus.

In contrast to the finding by Castro *et al.*,¹¹ in the present series the overall 5-year survival rate was 48 percent. Sixty-nine percent of the cancers were stage A, B₁, or B₂ (Astler-Coller). The relatively higher operative mortality (5 percent) and morbidity (22 percent), compared with operations for ordinary colorectal cancer,³⁰ may be related to the radiation effects.

Conclusion

Seventy-six cases of colon or anorectal cancer after pelvic irradiation for other malignant or benign lesions were reviewed. There were 13 men and 63 women with a mean age of 65 years. Sixty-seven percent of the patients had received irradiation for a gynecologic malignancy. Colon or anorectal cancer developed a mean of 15.2 years after irradiation with a peak frequency between five and ten years. Eighty-five percent of the patients had a mild to prominent radiation reaction around the cancer. Twenty-six percent of the 72 adenocarcinomas were mucinous adenocarcinoma. Only 17 percent of patients presented with symptoms of radiation proctitis, and the mean radiation dosages were lower than usual. High radiation dosage and severe radiation damage may not be essential for radiation-associated colorectal cancer. The overall five-year survival rate was 48%. Close surveillance of the colon and anorectal region of these high-risk patients at five years after irradiation is indicated.

References

- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
- Slaughter DP, Southwick HW. Mucosal carcinomas as a result of irradiation. *Arch Surg* 1957;74:420-9.
- Smith JC. Carcinoma of the rectum following irradiation of carcinoma of the cervix. *Proc R Soc Med* 1962;55:701-2.
- Black WC III, Ackerman LV. Carcinoma of the large intestine as a late complication of pelvic radiotherapy. *Clin Radiol* 1965;16:278-81.
- Quan SH. Factitial proctitis due to irradiation for cancer of the cervix uteri. *Surg Gynecol Obstet* 1968;126:70-4.
- Pemberton M, Lendrum J. Squamous-cell carcinoma of the caecum following ovarian adenocarcinoma. *Br J Surg* 1968;55:273-6.
- Localio SA, Stone A, Friedman M. Surgical aspects of radiation enteritis. *Surg Gynecol Obstet* 1969;129:1163-72.
- DeCosse JJ, Rhodes RS, Wentz WB, Reagan JW, Dworken HJ, Holden WD. The natural history and management of radiation induced injury of the gastrointestinal tract. *Ann Surg* 1969;170:369-84.
- MacMahon CE, Rowe JW. Rectal reaction following radiation therapy of cervical carcinoma: particular reference to subsequent occurrence of rectal carcinoma. *Ann Surg* 1971;173:264-9.
- Bhagabati JN, Zaman N. Carcinoma of sigmoid colon occurring after radiation therapy for carcinoma of the cervix: report of a case. *Indian J Med Sci* 1973;27:143-5.
- Castro EB, Rosen PP, Quan SH. Carcinoma of large intestine in patients irradiated for carcinoma of cervix and uterus. *Cancer* 1973;31:45-52.
- Cunningham MP, Wilhoite R. Radiation-induced carcinoma of the transverse colon: report of a case. *Dis Colon Rectum* 1973;16:145-8.
- Qizilbash AH. Radiation-induced carcinoma of the rectum: a late complication of pelvic irradiation. *Arch Pathol Lab Med* 1974;98:118-21.
- Greenwald R, Barkin JS, Hensley GT, Kalser MH. Cancer of the colon as a late sequel of pelvic irradiation. *Am J Gastroenterol* 1978;69:196-8.
- O'Connor TW, Rombeau JL, Levine HS, Turnbull RB Jr. Late development of colorectal cancer subsequent to pelvic irradiation. *Dis Colon Rectum* 1979;22:123-8.
- Sabio H, Teja K, Elkon D, Shaw A. Adenocarcinoma of the colon following the treatment of Wilms tumor. *J Pediatr* 1979;95:424-6.
- Martins A, Sternberg SS, Attiyeh FF. Radiation-induced carcinoma of the rectum. *Dis Colon Rectum* 1980;23:572-5.
- Shamsuddin AK, Elias EG. Rectal mucosa: malignant and premalignant changes after radiation therapy. *Arch Pathol Lab Med* 1981;105:150-1.
- Echave V, Madarnas P, Devroede G, Reesal M, Pearl G, Melancon F. Colonic carcinoma subsequent to radiation therapy. *Coloproctology* 1982;4:230-2.
- Dickson RJ. Late results of radium treatment of carcinoma of the cervix. *Clin Radiol* 1972;23:528-35.
- Smith PG, Doll R. Late effects of X-irradiation in patients treated for metropathia haemorrhagica. *Br J Radiol* 1976;49:224-32.
- Reimer RR, Hoover R, Fraumeni JF Jr, Young RC. Second primary neoplasms following ovarian cancer. *J Natl Cancer Inst* 1978;61:1195-7.
- Brown WM, Doll R. Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis. *Br Med J* 1965;2:1327-32.
- Rubin P, Ryplansky A, Dutton A. Incidence of pelvic malignancies following irradiation for benign gynecologic conditions. *Am J Roentgenol* 1961;85:503-14.
- Palmer JP, Spratt DW. Pelvic carcinoma following irradiation for benign gynecological diseases. *Am J Obstet Gynecol* 1956;72:497-505.
- Sandler RS, Sandler DP. Radiation-induced cancers of the colon and rectum: assessing the risk. *Gastroenterology* 1983;84:51-7.
- Beebe GW, Kato H, Land CE. Studies of the mortality of A-bomb survivors. VI. Mortality and radiation dose, 1950-1974. *Radiat Res* 1978;75:138-201.
- Kato H, Schull WJ. Studies of the mortality of A-bomb survivors. VII. Mortality, 1950-1978. Part I: Cancer mortality. *Radiat Res* 1982;90:395-432.
- Denman DL, Kirchner FR, Osborne JW. Induction of colonic adenocarcinoma in the rat by X-irradiation. *Cancer Res* 1978;38:1899-1905.
- Lisco H, Brues AM, Finkel MP, Grundhauser W. Carcinoma of the colon in rats following the feeding of radioactive yttrium. *Cancer Res* 1947;7:721.